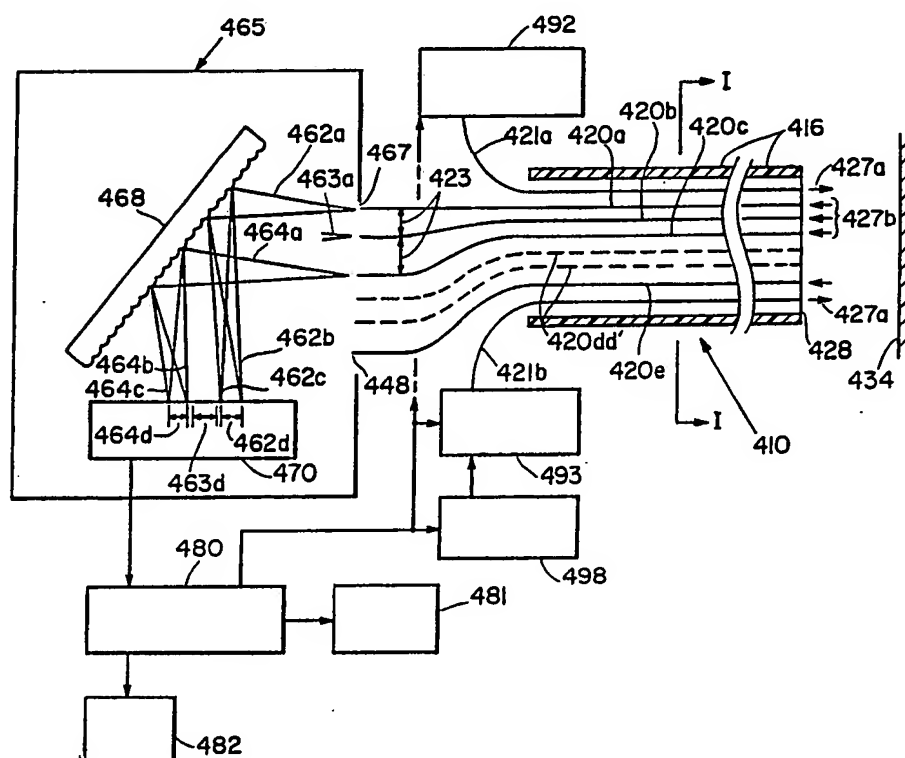


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## (54) Title: CATHETER SYSTEM FOR IMAGING



## (57) Abstract

A catheter system for imaging wherein optical fibers within a catheter are used to illuminate tissue for diagnostic purposes. Both spectroscopic and visual displays of the tissue are generated simultaneously. Fluorescence and Raman

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CATHETER SYSTEM FOR IMAGING

Technical Field

This invention relates to devices in which optical fibers are provided within a catheter which is coupled to a spectrometer with an imaging detector and  
05 diagnostic light is used to create a spectral image of the target tissue.

Background of the Invention

Optical spectroscopy is proving to be a powerful tool for probing the type and condition of tissue.  
10 Images of tissue may be recorded remotely, and in vivo, using flexible coherent bundles of optical fibers. Spectra may be recorded in a conventional way using a scanning monochromator. But this is time consuming and inefficient in using the often weak  
15 signals associated with tissue spectroscopy, especially where fluorescence excessive intensity may damage tissue thermally and excessive fluence may damage tissue photochemically or by other means. A spectrograph fitted with an imaging device, such as a  
20 linear diode array, charge coupled device (CCD), charge injection device (CID), vidicon or other such imaging device, converts the entire dispersed spectrum into an electronic signal so that all the desired light is detected simultaneously. As the spectrograph  
25 may be connected to an optical fiber, the emitted

spectrum is recorded. The other end of the fiber may be placed in tissue or at the bottom of a well or in other remote locations, to collect the light carrying information about its environment. However, this  
05 device records only a spectrum, not an image. Similarly, coherent bundles of optical fibers transmit images from remote locations, which are recorded on similar electronic imaging devices for video display and storage. However, combining spectral analysis and  
10 imaging has proved more difficult.

There is a need for a means to spectrally record the entire image simultaneously. Instead of using a single optical fiber consider the use of an image from a coherent bundle of optical fibers that is placed at  
15 the entrance of a spectrometer. If the image was monochromatic, then a monochromatic image would also form on the imaging detector at a certain location, depending on the position of the grating, or other dispersing device. A spectrograph with an adequate  
20 flatness of field is assumed here. If a second color was added to the image, then a second image would form on the detector, displaced from the first image, but in some part overlapping the first, depending on the amount of dispersion. Any given detector element  
25 might be detecting light from one part of the image of one color, or another part of the image, of a different color. The output would be ambiguous. As more colors are added to the input image, a single element would detect more and more different parts of  
30 the image in different colors, with no intrinsic way to sort out the mixed data. The imaging detector will

obtain a quite unsuitable spectrally blurred or smeared image.

Fluorescence and laser induced fluorescence has been used to diagnose tissue type and condition. A  
05 wavelength of 480 nm excited fluorescence in the range of 500-650 nm has been used, whereby the ratios of peak and valley signals were useful to distinguish atheromateous plaque from normal artery wall. In Alfano, visible laser excitation induced fluorescence  
10 in cancerous and normal tissue, with emission over a range of 500-700 nm, which showed differences in the spectra for the tissues. However, other wavelengths of excitation and detection may be useful. Fluorescence emission characteristics of a particular chromo-  
15 phore tend to occur at the same wavelength, for a broad range of excitation wavelengths.

A different type of spectroscopy, termed Raman spectroscopy, depends on a frequency shift from the exciting laser line. The Raman spectral peaks will  
20 occur at a fixed frequency separation from the laser line, and, in principle, occur for any excitation wavelength. It is the frequency difference that is the most distinguishing feature. Raman spectroscopy has been used for identifying a wide range of sub-  
25 stances such as molecules in solution or in flames.

#### Summary of the Invention

In accordance with the invention, the optical fibers, the spectrometer, and the detector will be configured in a novel way so that information adequate  
30 to construct both image and spectra will be obtained.

consider a specific embodiment and number of optical fibers described below; but the invention need not be limited in this manner. A coherent optical fiber bundle comprised of 10,000 fibers in a square array, 055 having 100 columns of fibers side by side, with each column containing 100 individual fibers in vertical array. Each fiber has a 10 micrometer core and a 20um outer diameter, including cladding. The coherent bundle forms a square with a 2mm cross section at the 100 input or distal end. At the output end, the columns are separated one from another and spaced to a distance of 500um to form a rectangular array 2mm by 50mm. This array, or an image of the array is placed at the entrance of low-dispersion spectrometer which 15 is corrected to have adequate flatness of field and minimize other aberrations. For no magnification, the dispersion is chosen so that the spectral region of interest does not exceed 500um. This spectral region may be limited with filters to avoid overlap.

20 Dispersion in the horizontal plane will be assumed throughout this description, but it need not be limited to this plane. Impinging on a 2-dimensional image detector of adequate dimension (at least 50mm wide in this case), is such that the dispersed spectrum of each column will not overlay that of the next 25 column. For a detector with a 20um square element, each pixel element, corresponding to each optical fiber, will be dispersed over 25 detector elements, subdividing the spectrum into 25 resolution elements.

30 Thus, each of the 10,000 optical fibers will couple to a separate 25 elements of the detector which has

250,000 elements, so that each spectrum may be recorded individually without overlapping another spectrum.

For a more compact system with a square detector array, columns of fibers could be placed one below another in groups. For example, if 5 columns from the coherent bundle were combined into a single column 500 fibers each 10mm long, and there were 20 such columns spaced 500um apart, this would form a square array 10x10mm and could be projected onto a square detector with or without magnification. Without magnification each image pixel would be dispersed over 25 detector elements. A larger number of detector elements, and appropriate adjustments of column spacing and magnification would allow for more spectral resolution elements per pixel.

Another arrangement of optical fibers would consist of subdividing the square array into a square block rather than columns. For example, a 5x5 block of fibers could be relocated, and arranged into a 25 fiber column. The image would be dispersed onto a square portion of the detector 25 elements high by 25 elements wide. The adjacent block of optical fibers would be imaged onto a corresponding adjacent block of the detector. This would minimize crosstalk problems between widely separated parts of the image, as adjacent parts of the image are observed by adjacent parts of the detector. With this type of arrangement, a lower resolution image could be obtained if desired. The block of optical fibers and corresponding block on the detector might be treated as a single pixel. Of

course, any arrangement of optical fibers of the distal end might be matched in many ways to the image detector. For example, a single linear array could be used for a small number of optical fibers.

05       Special optical coupling elements may be installed between the output of the optical fiber bundle and the spectrometer detector. Anamorphic elements, such as cylindrical lenses or prisms, can expand the image more in one dimension than another.  
10       The rectangular 2mm x 50mm image previously described could be changed to a rectangle of different dimensions, or even a square. Likewise, the round image of a single optical fiber can be made oblong to match a rectangular element on a detector array.

15       Optical fibers are not essential to this concept, however the image may be subdivided by small mirrors or beamsplitters to fall on different parts of the detector.

          An image may also be spectrally resolved with a  
20       somewhat different type of apparatus. The image from the optical fibers is collimated and sent through a travelling Michaelson interferometer. A single pixel undergoes constructive and destructive interference as the travelling mirror moves; the recorded spectrum as  
25       a function of time is converted by Fourier transform to a wavelength spectrum. If however, the detector is replaced by an imaging device, such as a CCD, then every pixel is subject to the interferometer. The imaging device needs to be "read out" many times as  
30       the mirror scans, so as to provide enough data for an accurate transform to be obtained. As an example, the



CCD would be read out entirely twenty times for each wavelength of travel of the mirror. The time to acquire a spectral image may become significant. Also, substantial computing power should be needed to  
05 do the Fourier transform of the data for thousands of pixels in a small amount of time.

Another system which can spectrally filter an image from an optical fiber bundle would be comprised of filters and beamsplitters. The light from the  
10 image may pass through a series of beam splitters to fall on one or more imaging detectors. Dichroic beamsplitters will separate the light into various colors with minimal losses. Absorbing filters may also be interposed in the light path to select  
15 wavelengths, however these are less efficient. Multiple images, each of a different color, may impinge on a single imaging detector.

It is anticipated that there will be a broad range of uses for this type of spectroscopic imaging  
20 device, both within and outside of the medical field.

We have found ultraviolet excited laser induced fluorescence provides a useful diagnostic for arterial tissue distinguishing normal from plaque. Experiments used wavelengths from 220 nm to 330 nm for excitation,  
25 with detection ranging from close to the laser wavelength to 750 nm. Several useful laser induced fluorescence diagnostics were found. Two peaks and a valley in the range of 370-470nm are useful for distinguishing normal and plaqued artery. Even after  
30 laser ablation damage, the valley of about 420 nm persists. It is likely due to the Soret band of

porphyrin, probably from heme. These features should also be useful for identifying other types of tissue as well. Weak LIF emission also occurred in the range 600-700 nm with a peak at 650 nm, for the wide range  
05 of ultraviolet excitation. Also, ultraviolet wavelengths shorter than 320 nm excite a broad fluorescence probably due to tryptophan, which for 220-280 nm excitation ranges from 290-380 nm with a maximum of about 335 nm. The intensity, and the fluorescence  
10 lifetime (typically about 3 nsec) varies with tissue type and may provide a useful diagnostic.

A Raman peak useful for diagnostic occurs at about  $3300\text{cm}^{-1} \pm 150\text{cm}^{-1}$ . Although excitation wavelengths in the range 220-228 nm were used, Raman  
15 scattering occurs for all excitation wavelengths; it is the frequency shift that is the distinguishing characteristic. Plaque showed a much stronger Raman signal than did the healthy arterial media. The frequency shift remained relatively constant as the  
20 excitation frequency was changed, proving that the spectrum is a Raman process, and not LIF. This signal persisted after laser ablation damage, and was useful in determining that when plaque layer was penetrated, the underlying healthy media gave a weaker signal.  
25 This change in Raman signal strength could be used as a feedback control diagnostic to signal that plaque has been removed, and that tissue ablation may be halted.

Brief Description of the Drawings

Figure 1 is a broken longitudinal cross-section of the imaging catheter, spectrometer and a block diagram of the computer and outputs, illustrating a preferred embodiment of the invention.

Figure 2 is a cross-sectional view of the imaging catheter.

Figure 3 is an optical schematic illustrating target illumination by the same optical fibers used to collect the emitted or reflected light, and illustrates optical imaging of the proximal end of the catheter onto the spectrometer aperture.

Figure 4 is an optical schematic showing the use of dual detection systems.

Figure 5 is an optical schematic showing the use of a Michaelson interferometer.

Figure 6 is an optical schematic illustrating the use of a lens to image the target onto the distal end of the catheter.

Figure 7 shows fluorescence of a normal aorta artery wall stimulated by 329nm excitation. The left hand scale (ordinate) is intensity of fluorescence signal (figures 7-10 use the same conditions).

Figure 8 shows plaque fluorescence under the same conditions of Fig. 7. This is a soft plaque, mainly fibrous and fatty. The peaks have shifted slightly in wavelength and in the height ratio; but the valley is much less deep.

Figure 9 shows the spectrum whereby an argon ion laser, using multiple shots, has ablated through the

1-2mm plaque layer to reach the normal media beneath. Total dosage was about  $5-10\text{J/mm}^2$ . The spectrum of the tissue at the bottom of the crater is shown. The spectral shape is somewhat altered, but a valley at  
05 about 425nm persists.

Figure 10 shows an adjacent region ablated by the argon ion laser, fewer exposures were made so the plaque was not penetrated. This spectrum is clearly distinguishable from Figure 9, showing that this is a  
10 useful diagnostic for determining when the plaque layer has been penetrated.

Figure 11 shows fluorescence from normal aorta using 320nm excitation.

Figure 12 shows fluorescence from plaque under  
15 the same conditions. This shows that useful diagnostic information can be obtained for various excitation wavelengths.

Figure 13 shows normal artery excited by 220nm, yielding a fluorescence peak of about 330nm, most  
20 likely due to tryptophan. A fluorescence lifetime of about 3nsec was observed; this may also yield useful diagnostic information.

Figure 14 shows plaque on the same artery sample, under the same conditions. As for Figure 13, the peak  
25 has less intensity. Any UV wavelength shorter than 330nm excites this fluorescence.

Figure 15 using 280nm excitation, a weak peak at 650nm is seen. The detection sensitivity is high so the tryptophan peak is off scale. This is for plaque.

Figure 16 shows a fluorescence spectrum for normal tissue, under the same conditions as for Figure 15 showing greater intensity for the 650nm peak.

05 Figure 17 shows a Raman peak at about 244nm. The laser line is about 225nm. (A correction of -2nm is needed for all following Figures 17-22). There is an intensity scale change at about 233nm. This spectrum is for soft plaque, fibrous and fatty. The frequency shift is about  $3,320\text{cm}^{-1}$ . This corresponds to an O-H  
10 stretching frequency, or possibly that of N-H.

Figure 18 shows a spectrum for normal arterial media on the same tissue sample. The Raman peak is much weaker.

Figure 19 shows a spectrum of calcified plaque  
15 which has been irradiated with about  $2\text{ Joules/mm}^2$  from an argon ion laser, 514nm. The strong Raman peak at 244nm is present, with a frequency shift of  $3,320\text{cm}^{-1}$ .

Figure 20 shows a different excitation wavelength for one laser 222nm; the Raman peak has moved also  
20 proving that this is Raman and not fluorescence emission. The difference in frequency is about  $3,290\text{cm}^{-1}$ , which is unchanged within experimental error..

Figure 21 shows a Raman spectrum of plaqued aorta  
25 artery wall whereby the plaque has been ablated away as described for Figure 9. The Raman peak at about 242nm is weak, indicating that the overlying plaque has been removed.

Figure 22 shows Raman spectrum of ablated plaque  
30 which was not penetrated, similar to that described for Figure 10. The Raman peak at about 242nm is

strong, indicating that there is still plaque at the bottom of the crater. A weak "shoulder" peak is seen at about 232nm corresponding to about a  $1600\text{cm}^{-1}$  Raman shift which could be a carbonyl stretching frequency; 05 this may also have useful diagnostic properties, but better laser light rejection will be needed to examine it.

#### Detailed Description of the Invention

Figure 1 shows a preferred embodiment of the 10 invention. The catheter 410 is shown in broken longitudinal section. It has a distal end 428 and a proximal end 448 and contains 10,000 imaging optical fibers or similar light conduits in a 100 by 100 square array. Optical fibers 420 a,b,c,e are shown, with 420 dd' indicating the large number of additional optical 15 fibers in the array. Illuminating optical fibers 421 a,b are coupled to a laser source 492 or a conventional light source 498 with wavelength selection 493 comprised of filters, a monochromator, 20 or similar device. Illuminating light 427 a emerges from illuminating fibers 421 a,b and falls on the target tissue or sample 434, which may or may not be in contact with the catheter. Light returning 427 b from the sample is collected by the fibers 420 a-e to 25 be delivered to the spectrometer 465.

Since this is a cross-sectional view, each optical fiber illustrated actually represents a column of 100 optical fibers. These columns of fibers are physically separated by a distance indicated by arrow 30 423 at the proximal end 448 of the catheter and all

are placed at the entrance aperture 467 of the spectrometer 465. The emitted rays of light from each column of fibers 420 a-e fall on the grating 468 and are dispersed. The grating may be self focussing as shown, or the spectrometer 465 may contain additional optics to produce the image at the two dimensional detector array 470. Because of the physical separation 423 between fibers, the spectrally dispersed images 462d, 463d, and 464d of the fibers will be physically separated on the detector array 470. Light rays 462a spreading from fiber 420a are dispersed in the horizontal plane with the longer wavelength rays 462c and shorter wavelength rays 462b impinging on the detector 470 over a range of 462d. Similarly, rays 464a from fiber 420c are dispersed to long 463d. These spectral ranges do not overlap, so that spectra are recorded separately.

From detector 470, the electronic signals go to the computer and controller 480, where they are processed and displayed as a spectral map on terminal 482 or output as hard copy on 481. The computer may also control light source 498, scannable monochromator or changeable filter wavelength selector 493, or laser light source 492. Both excitation and emission spectra may be obtained. The computer 480 records the spectrum from each optical fiber to construct the spectrum from each optical fiber to construct the spectral image; the light from each fiber 420 a-e represents a pixel of data for the image. With suitable algorithms, the spectra are compared to stored spectra and converted to diagnostic information

about each pixel, such as tissue type, and presence or absence of disease. An image showing such a condition is displayed on the monitor 482, or printed out on 481.

05        Figure 2 shows a cross section of the optical fiber catheter 410 in a preferred embodiment, with the array at 100 columns of fibers containing one hundred fibers each. The first column comprises the fibers 520a, 521a, 522a, 524a, and with more fibers indicated  
10 by dotted line 523a. The second column has fiber 520b at the top, and the third column has fiber 520c, the last column has fiber 520e at the top. Additional columns are indicated by dotted lines 520 d-d'.  
Illumination fibers 421 are shown at the periphery,  
15 although they may also be located between the columns. An optional inner sleeve surrounds the fibers. The whole is contained in an outer tube or catheter 416. .

Figure 3 is an alternate embodiment where by the proximal end 448 of the catheter is imaged onto the  
20 aperature 467 of the spectrometer 465. Lenses 541 and 542 make, the image, but mirrors or other optics may also be used for the purpose. Rays 564a from the optical fibers are collimated 564b and focussed 564c. Optional beamsplitter 552, which may be dichroic or  
25 partially reflecting, allows illuminating light 594a from source 592 and coupling selector 546 to be coupled directly into the optical fiber bundle 520. The rays 594b are focus 594c onto the proximal end of the catheter 448. Selector 546 may contain optics and  
30 beam directions to allow coupling into any or all of the optical fibers 420 a-e in the catheter 410.



Figure 4 shows an alternate embodiment using two spectrometers. The light emerges from the proximal end 548 of the catheter 410. The columns of fibers in the bundle 520 need not be separated. Rays 564a are collimated 564b by lens 541a and are divided by partially reflecting beamsplitter 552a. Some of the light rays 564c form an image on the aperature 467a of spectrometer 465a. Some of the 564d pass through image rotating prism 549 or similar optical system. The rays 564e now rotated through an angle such as 90°, reflect from optional mirror 548 and are converged 564f by lens 543a to form an image on aperature 467b of spectrometer 465b. As in Figure 1, the two spectrometer detectors are connected to a computer where the data from the two spectrally dispersed images can be processed.

Figure 5 shows an alternate embodiment using a Michaelson interferometer. The proximal end 548 of the optical fiber bundle 520 has light rays 564a which are collimated by lens 541b, entering into Michaelson-type interferometer comprised of beam splitter 552b, fixed mirror 545 and movable mirror 546. The exiting lights is focussed by lens 542b, and the rays 564g are imaged onto two dimensional detector 570. The computer 580 is capable of performing Fourier transforms of the data from all of the elements on the detector. The detector 570 need have only as many elements as there are optical fibers in the bundle 520, since this is a non-dispersive system.

Figure 6 shows an alternative embodiment with collection optics at the distal end of the catheter.

Lens 441 collects light rays 560a emanating from tissue 434 and focusses the rays 460b onto the distal surface 428 of the catheter 410, for illustration, the rays corresponding to optical fiber 420c are shown.

05 An optional optical shield 412 may be used to protect the optics.

In alternate embodiments, any number of optical fibers may be arrayed in the catheter in a square, hexagonal, circular, or other patterns. In Figure 4,  
10 the beam is divided into two components to be directed into two spectrometers. Additional beamsplitters or mirrors may be used to further subdivide the beam before going to the spectrometers. Other coupling optics, represented by those in Figure 3, may be used  
15 to magnify the image or expand it anamorphically to better suit the shape of the detector. Columns of optical fibers may be combined or separated so that the number of columns at the proximal surface is not the same as the number in the catheter, and the number  
20 of fibers within a column may also be changed. This will better match the geometry of the fiber array to that of the detector. More than one detector array may be used to obtain adequate coverage of the dispersed spectral image. This device may be used for  
25 medical imaging on any application where it is desirable to obtain both spectral and spatial imaging.

Whole arterial wall was placed in a capped fused silica cuvette, flush against the face, with moist clean paper behind the tissue to prevent drying.  
30 Pulsed ultraviolet laser light was used to excite fluorescence in the tissue. The fluorescence was

collected with fused silica optics and passed through a scanning double monochromator onto a photomultiplier. After gated integration, the signal was stored in a computer.

105       Excitation with about 329nm generated fluorescence from the laser wavelength to the sensitivity limit of the photomultiplier at about 700nm. Peaks were observed at about 395 and 450nm  $\pm$  10nm with a valley at 425 nm. The valley was deep for  
110 normal artery wall and shallow for plaque. Ablation damage from high power exposure with an argon ion laser upon the tissue altered the spectra, making the valley shallower in both cases. But differences remained, showing that diagnostic difference persists  
15 after laser damage. The valley is probably due to reabsorption by the Soret band of porphyrin, probably from heme. Shorter wavelength excitation using wavelengths as short as 220nm excited strong fluorescence at 335nm, most likely from tryptophan. A  
20 fluorescence lifetime of a few nanoseconds was observed for this emission and for other emission wavelengths as long as 550nm. The intensity and time resolved fluorescence characteristics of these spectra should provide tissue diagnostic information. Weak  
25 emission at 600-700nm, with a peak about 650nm, also appearing to be a useful diagnostic and occurs for all ultraviolet excitation.

For fluorescence spectroscopy, the molecular chromophore is put into an excited electronic state by  
30 absorption of a photon of light. The emission is characteristic of the particular chromophore; the peak

wavelength tends to remain constant when the excitation wavelength is changed. But excitation wavelength must match the chromophore absorption band.

05 Raman spectroscopy, which probes the vibrational energy levels of a molecule, eliminates this problem as almost any wavelength can be used. Due to the vibrational transitions of molecules contained in the material under study, light incident upon the material is inelastically scattered thereby transferring energy  
10 to the molecule and typically causing a decrease in the frequency of the scattered light.

The use of Raman spectroscopy for diagnostic purposes in distinguishing artery wall from atheromatous plaque via an optical fiber bundle  
15 disposed in a catheter is claimed.

Excitation at shorter wavelengths, particularly around 220nm, yielded a Raman signal with about a 3300  $\pm$ 150 wavemeter Stokes shift. This Raman signal was much stronger for plaque than for healthy artery wall.  
20 Since the shift is constant and independent of the excitation wavelength, it is a Raman signal. Such Raman signals should occur for all excitation wavelengths, although it is more difficult to observe when there is strong fluorescence emission also. The Raman  
25 signals persisted after the tissue was ablated with a high power argon ion laser. When the argon laser ablated an overlying layer of plaque, exposing normal media underneath, the Raman signal was substantially reduced, indicating that this signal is a useful  
30 diagnostic for determining when the plaque layer has been penetrated.

The Figures 17-22 show the data which illustrates the use of the Raman diagnostic for distinguishing plaque from underlying media. For the diagnostic to be useful for monitoring an ablation process, spectral differences should be present after ablation. Although the spectra of normal arterial tissue change to some extent after ablation has occurred, the plaque and healthy media can still be distinguished. In addition, the changes which occur as a result of ablation can be useful as a tissue damage monitor. Most important, however, is a means to determine when the plaque has been penetrated, and that media has been reached so that a signal can be generated to warn the operator that the process should stop; or the signal could be used as a feedback control to terminate laser firing through the particular optical fiber automatically.

Since the Raman scattering generally occurs from a relatively simple functional group, in this case the hydroxyl group (OH) or perhaps a nitrogen-hydrogen (NH) bond, it is probably quite photochemically and thermally stable, and resists laser damage. This is unlike the case for laser induced fluorescence which generally involves molecular chromophores and are more likely to suffer such damage. This makes the Raman spectra a promising new diagnostic tool for monitoring a tissue ablation or treatment process.

Raman scattering occurs for many frequencies as well. A signal is observed of about  $1600\text{cm}^{-1}$ , but is partially obscured by scattered laser light passing

through the scanning monochromator. This frequency shift may also prove to be a useful diagnostic.

05 In order to more accurately determine the frequency shift, the monochromator was scanned over the laser line, with the light-detecting photomultiplier adjusted to low gain. About 5-8 nm past the laser line (longer wavelength), the photomultiplier gain is greatly increased, resulting in a sharp rise in the signal on each Raman scan.

10 The following data taken from a number of scans prove that the peak is a Raman peak, and is not due to laser induced fluorescence.

<u>Spectrum</u> <u>Number</u>	<u>Laser</u> <u>Wavelength</u> <u>cm<sup>-1</sup></u>	<u>Raman</u> <u>Shift</u> <u>cm<sup>-1</sup></u>
1	43,971	3263
2	43,971	3298
3	43,191	3266
4	44,105	3197
5	44,165	3343
6	44,205	3228
7	44,245	3268
8	44,245	3177
9	44,420	3325
10	44,440	3314
11	44,440	3348
12	44,440	3365
13	44,504	3318
14	44,524	3167
15	44,524	3320
16	44,543	3323
17	44,823	3295
18	44,843	3263
19	44,843	3332
20	44,843	3366
21	44,863	3352

Even though the laser frequency ranges from 43,971cm<sup>-1</sup> to 44,863cm<sup>-1</sup>, for a difference of 892cm<sup>-1</sup>, the spectral shift remains relatively constant and shows no pronounced trend, proving that the observed peak is a Raman peak, not a fluorescence peak.

CLAIMS

1. An optical system which is capable of generating a spectrally resolved spatial image of tissue, comprised of:
  - 05 a catheter containing a plurality of optical fibers forming a bundle;
  - a laser coupled to the fibers to illuminate tissue with light;
  - dispersion means for dispersing light
  - 10 emitted by the sample and carried along the bundle to said means;
  - a detector array for receiving the dispersed light; and
  - 15 a computer for processing the received light such that the dispersed light is spectrally resolved and a displayable image of the illuminated tissue is formed.
2. The optical system of Claim 1 wherein the optical fibers are arranged within the catheter in a plurality of several separated columns such that the dispersed light exiting from one column does not overlap that from any other column on the array.
- 20 3. The optical system of Claim 1 wherein said dispersion means is comprised of:
  - 25 a self-focussing holographic grating.



4. A method of obtaining spectrally resolved spatial images comprising the steps of:

05           placing the distal end of an optical  
          multifiber catheter in contact with tissue  
          to be diagnosed;  
          passing light through illuminating  
          optical fibers onto the surface of said  
          tissue;  
10           collecting light emitted from said  
          tissue and delivering it to an entrance  
          aperture of a spectrometer with said optical  
          fibers in separated columns, such that the  
          dispersed spectra impinge on a detector  
          array without overlapping; and  
15           processing signals from said detector  
          array in a computer to generate a spatial  
          image of said tissue.

5. A method of diagnosis of the type of tissue in  
the artery, including distinguishing artery wall  
20   from atheromateous plaque, comprising the steps  
of:

          providing a catheter with a plurality  
          of optical fibers in which the distal end of  
          the catheter is enclosed by an optical  
25   shield having a fixed surface transparent to  
          light radiation and spaced from the ends of  
          said fibers wherein the proximal end of the  
          catheter and optical fibers may be coupled  
          to a source of optical radiation wherein the

radiation is capable of exciting  
fluorescence and scattering light;

05           inserting said catheter into an artery  
until the optical shield is brought into  
contact with a suspected arterial lesion or  
other tissue to be diagnosed;

10           selecting an optical fiber and coupling  
said light at a wavelength from the light  
source to the proximal end of said optical  
fiber whereby the light enters the proximal  
end of the optical fiber and is transmitted  
by the selected optical fiber to the distal  
end of said fiber out the optical shield and  
impinges on the suspected lesion, and the  
15           scattered light is returned to the proximal  
end of the selected optical fiber, and is  
coupled to a spectral analyzer wherein the  
scattered light excited by said light is  
analyzed to determine if the material con-  
tacted by the optical shield and, in  
20           particular, the portion irradiated by the  
incident light from the selected optical  
fiber is healthy arterial tissue or plaque  
or other material;

25           observing at the proximal end of the  
selected fiber a Raman signal within the  
scattered light excited by said light to  
analyze the spectral profile where peaks  
occur; and

30           determine from ratios of spectral peak  
heights of the light and the Raman signal

whether the tissue being analyzed is artery wall, plaque, blood or other tissue.

6. The method of diagnosis of Claim 5 wherein the light source is an argon ion laser.

- 05 7. A method of diagnosis of the type of tissue in an artery, including distinguishing artery wall from atheromateous plaque, comprising the steps of:

10 inserting a catheter containing a multiplicity of optical fibers into an artery, said catheter and fibers having proximal and distal ends with an optical shield means on the distal end of the catheter having an optically transparent enclosure with a distal output surface  
15 located a fixed distance from the distal ends of the fibers and extending over the end of the catheter and a distal surface for displacing body fluid such that direct contact can be made by said distal surface  
20 with such tissue within the artery and a laser source of light coupled to at least one of said fibers at a proximal end;

25 terminating said insertion when the optical shield is brought into contact with a suspected arterial lesion or other tissue to be diagnosed;

selecting an optical fiber coupled to said laser source and coupling said light to the proximal end of said optical fiber

whereby the light enters the proximal end of the optical fiber and is transmitted by the selected optical fiber to the distal end of said fiber out the optical shield and  
05 impinges on the suspected lesion to produce fluorescence and associated fluorescent light is returned to the proximal end of the selected optical fiber, and is coupled to a spectral analyzer wherein the fluorescent  
10 light is analyzed to determine if the material contacted by the optical shield and, in particular, the portion irradiated by the incident light from the selected optical fiber is healthy arterial tissue or  
15 plaque or other material, said analysis including:

- (i) observing at the proximal end of the selected fiber the fluorescence excited by said light to analyze the spectral  
20 profile in the range 360-500 nm, where peaks occur; and
- (ii) determining from ratios of fluorescence peak heights at about 395 nm and 450 nm and the valley at about 420 nm, whether  
25 the tissue being analyzed is artery wall, plaque, blood or other tissue.

8. The method of Claim 7 wherein the laser light source emits light at wavelengths in a range between about 300 nm to 340 nm.

9. The method of Claim 7 wherein less than 100 microwatts of average power is used from said laser source to excite fluorescence.
- 05 10. The method of Claim 7 including providing a beam splitter near the proximal end of the catheter to allow use of the same optical fiber for both delivery of incident light from the laser and return of fluorescent light to the spectral analyzer.

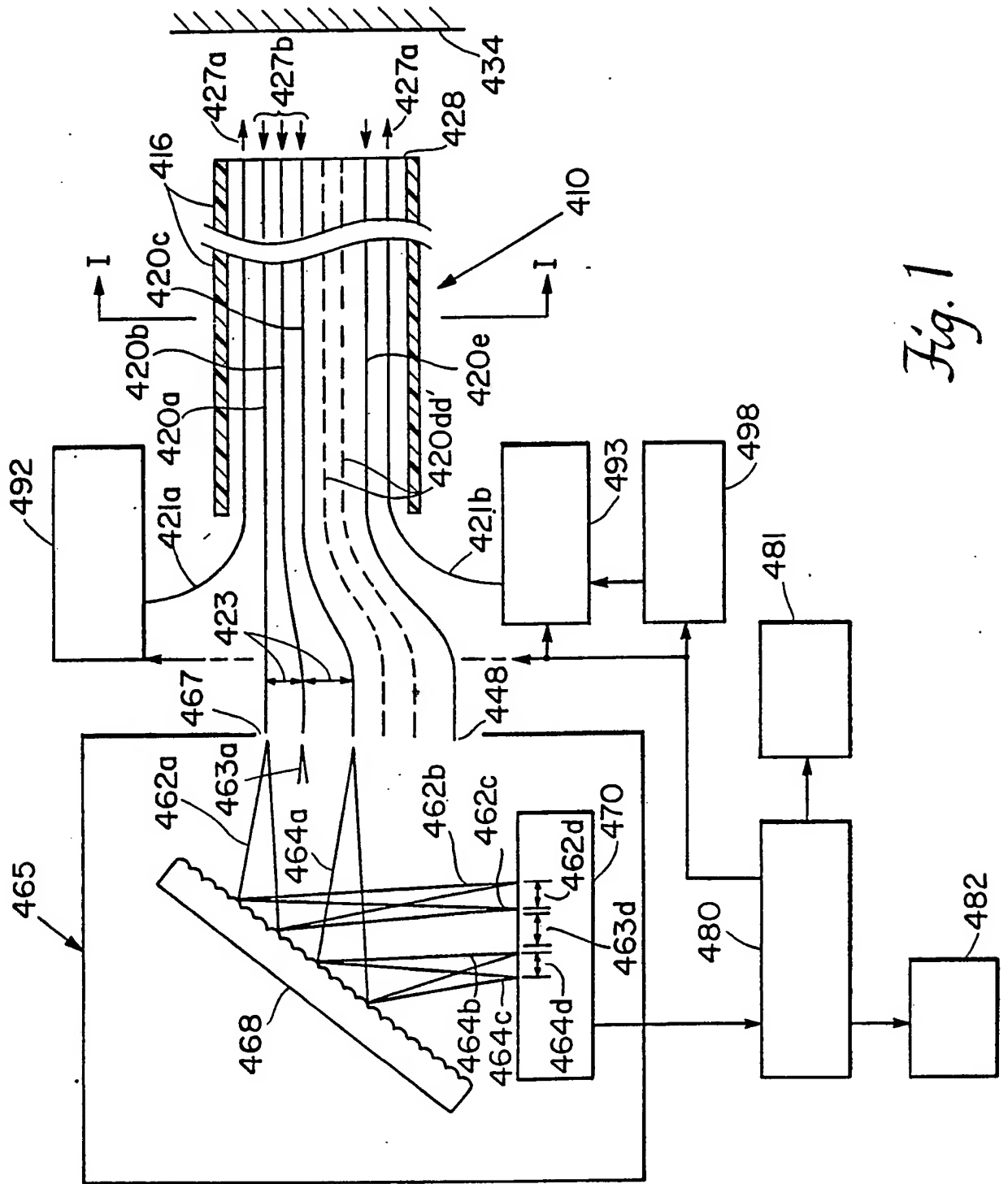


Fig. 1

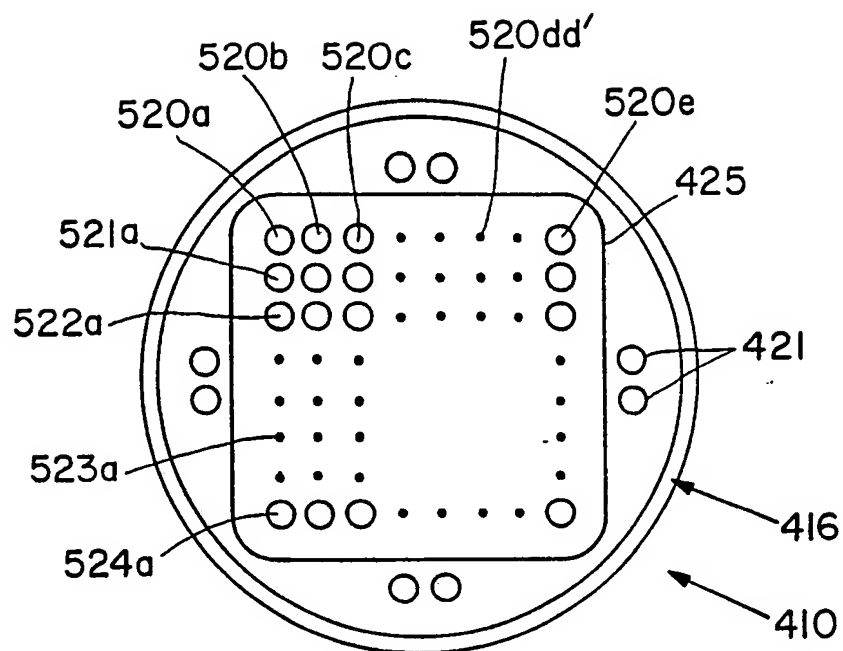


Fig. 2

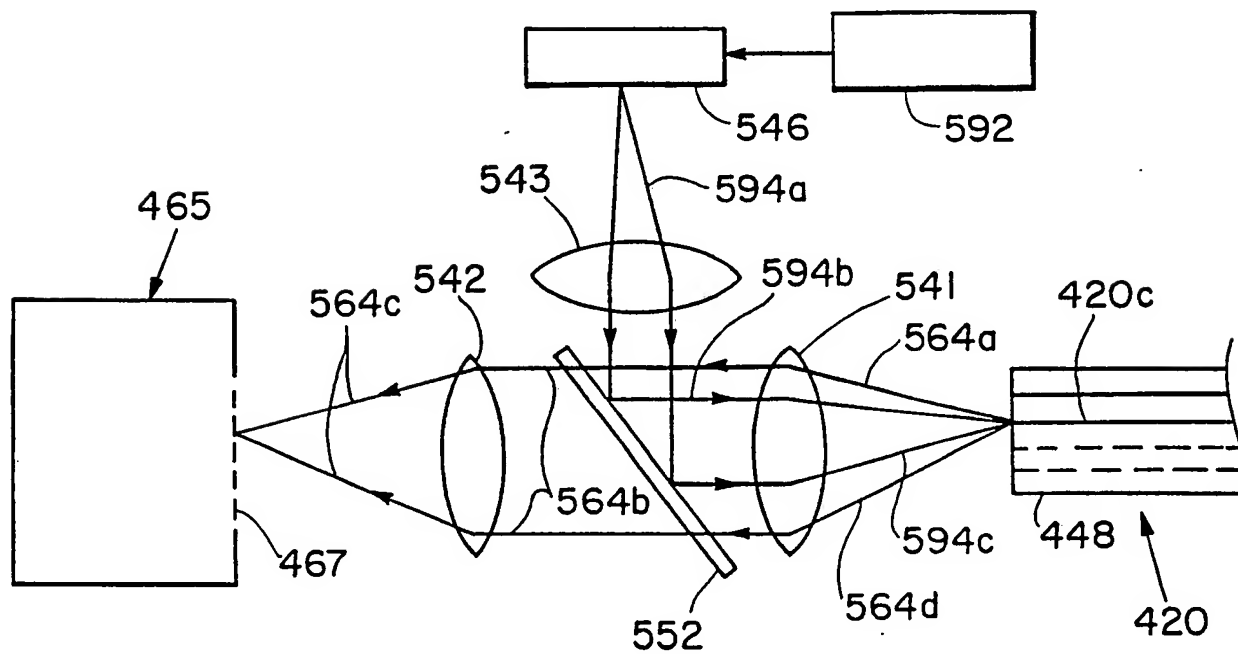
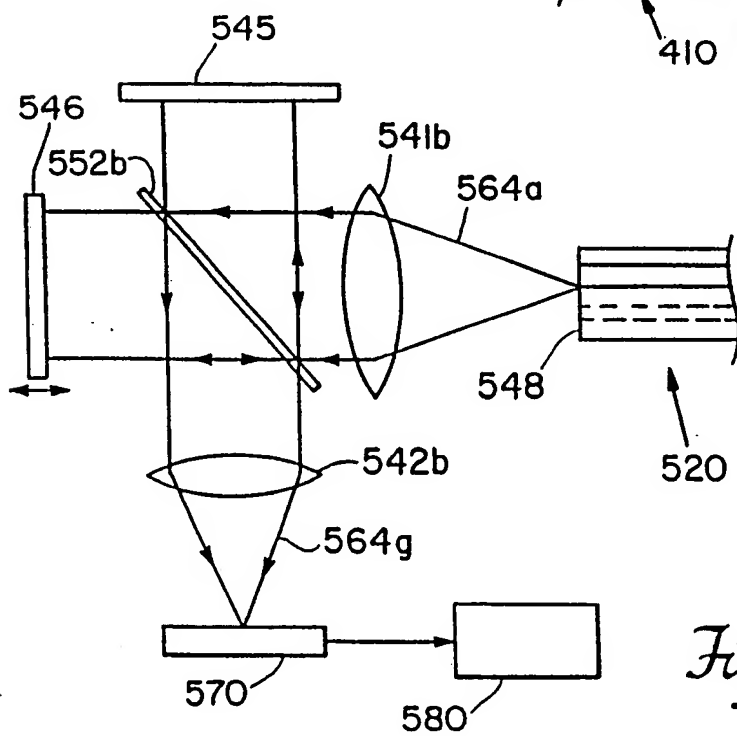
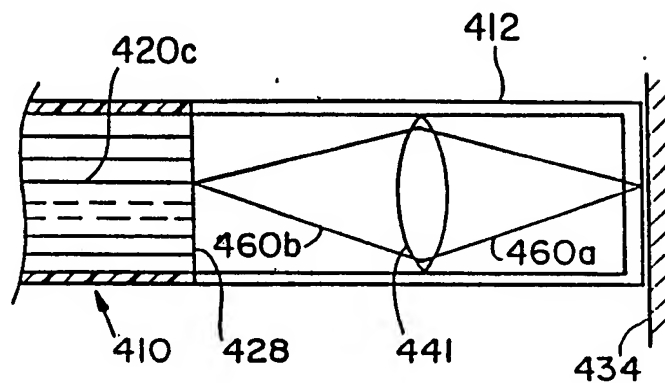
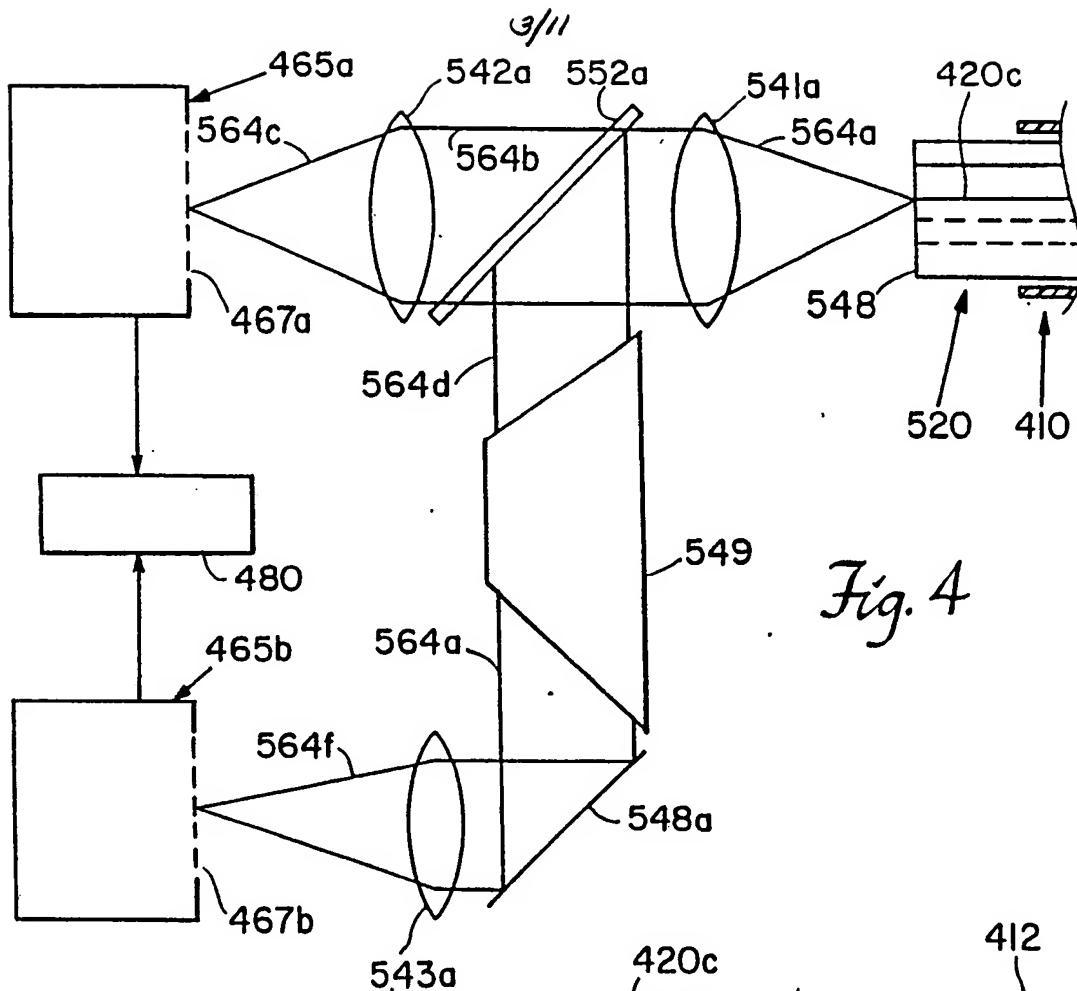
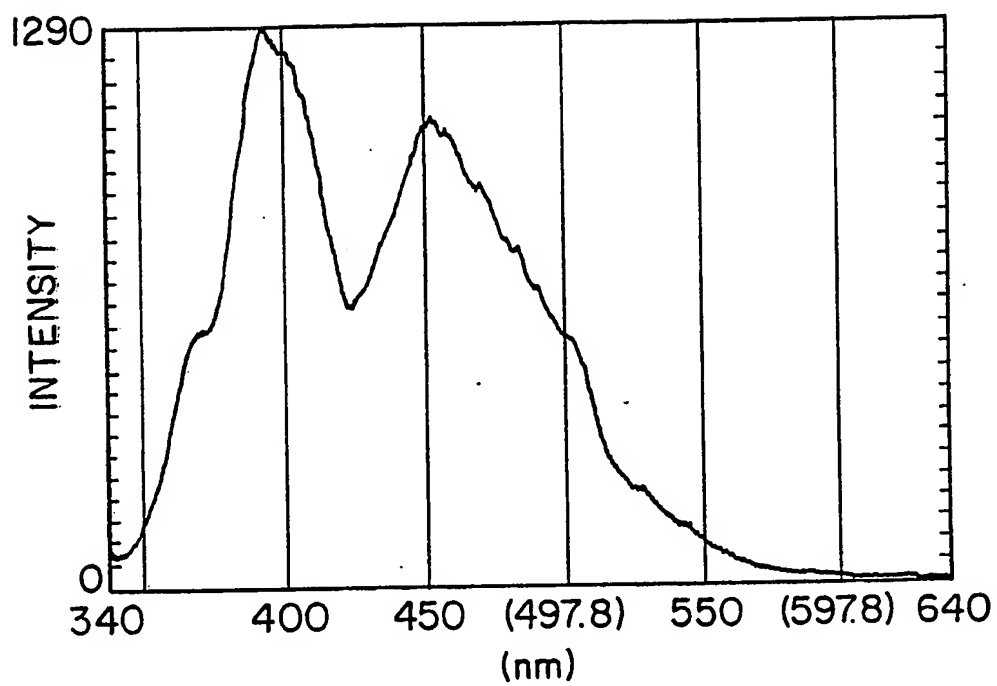
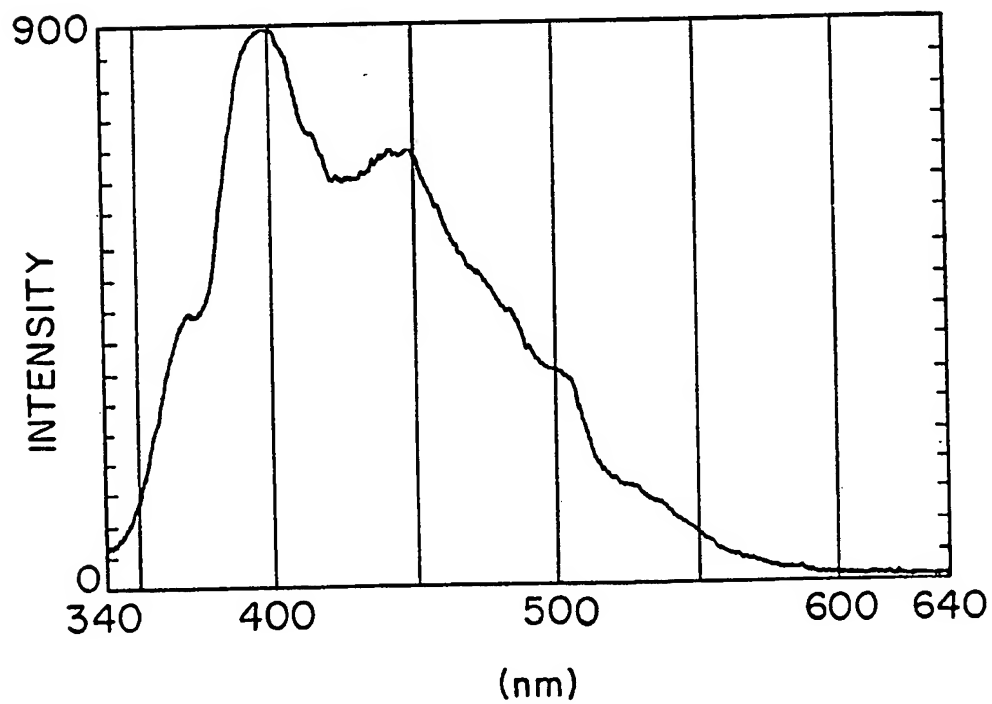
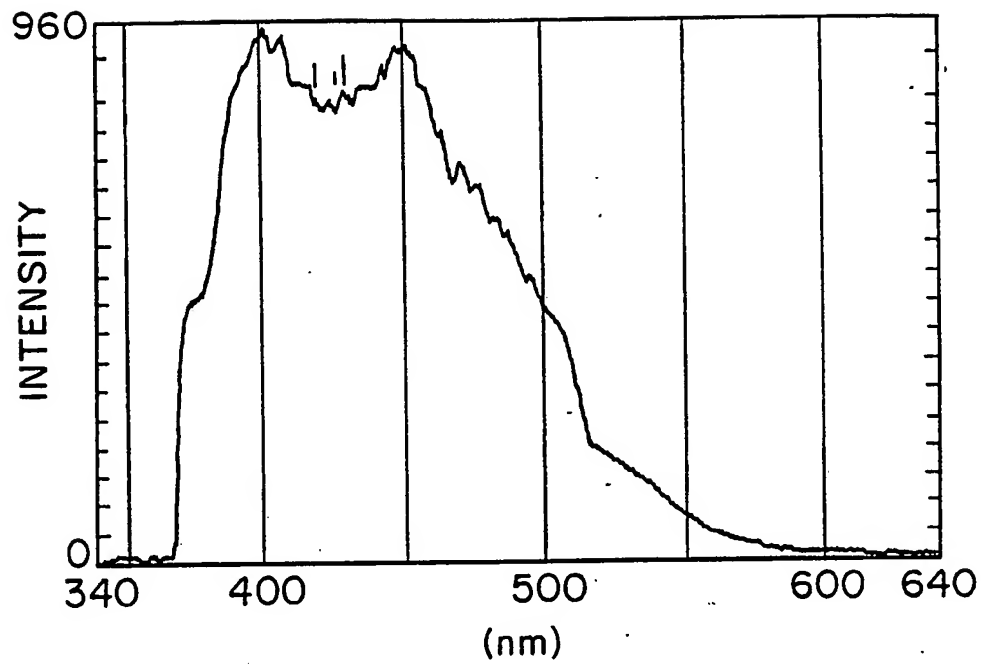
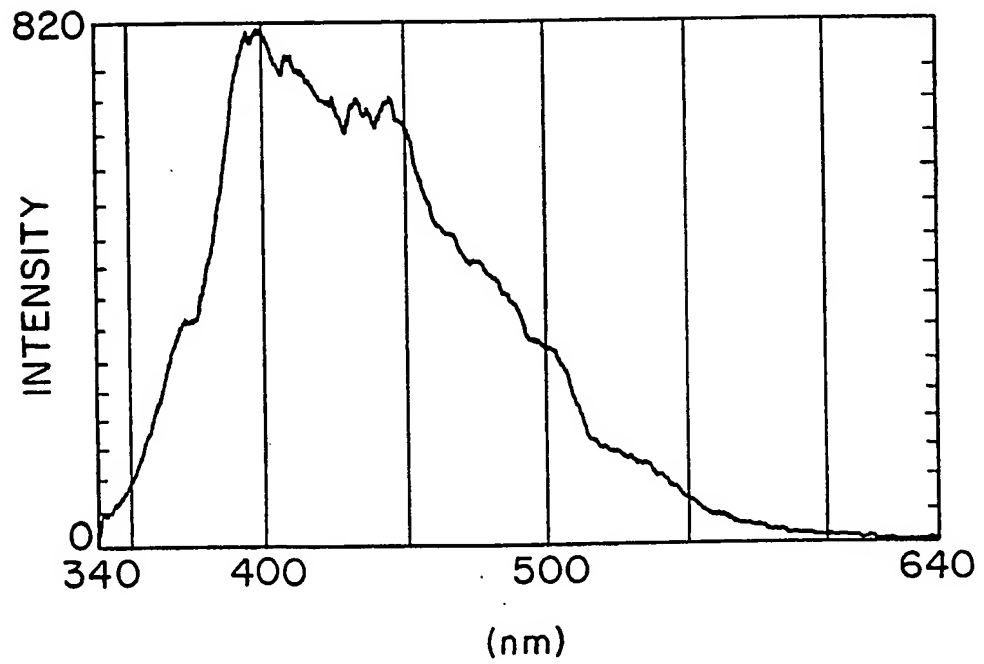


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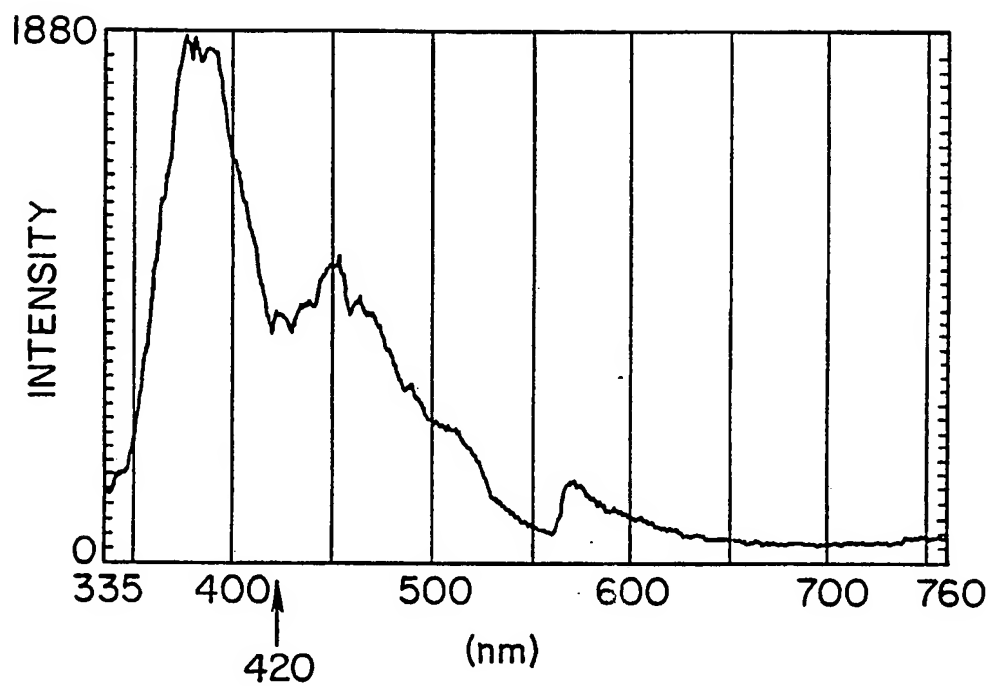




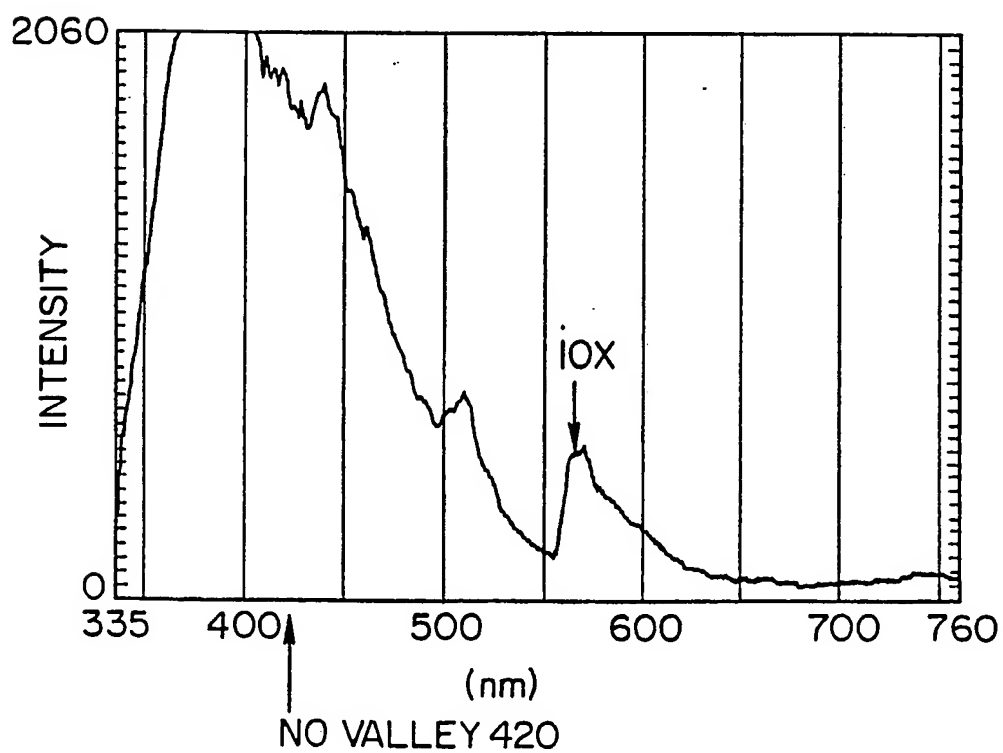
*Fig. 7**Fig. 8*

*Fig. 9**Fig. 10*

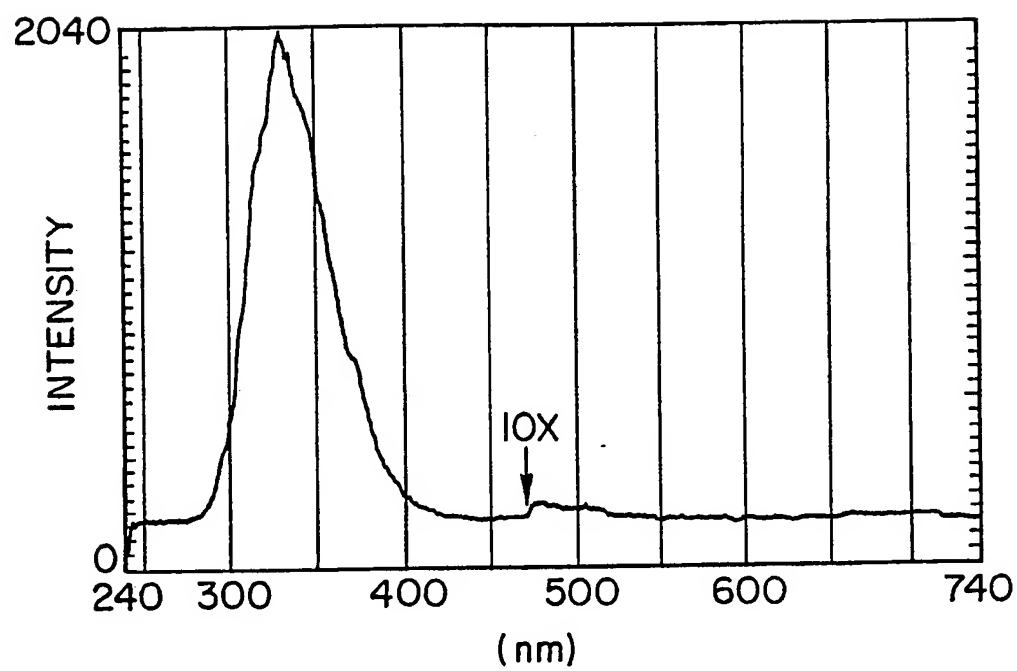
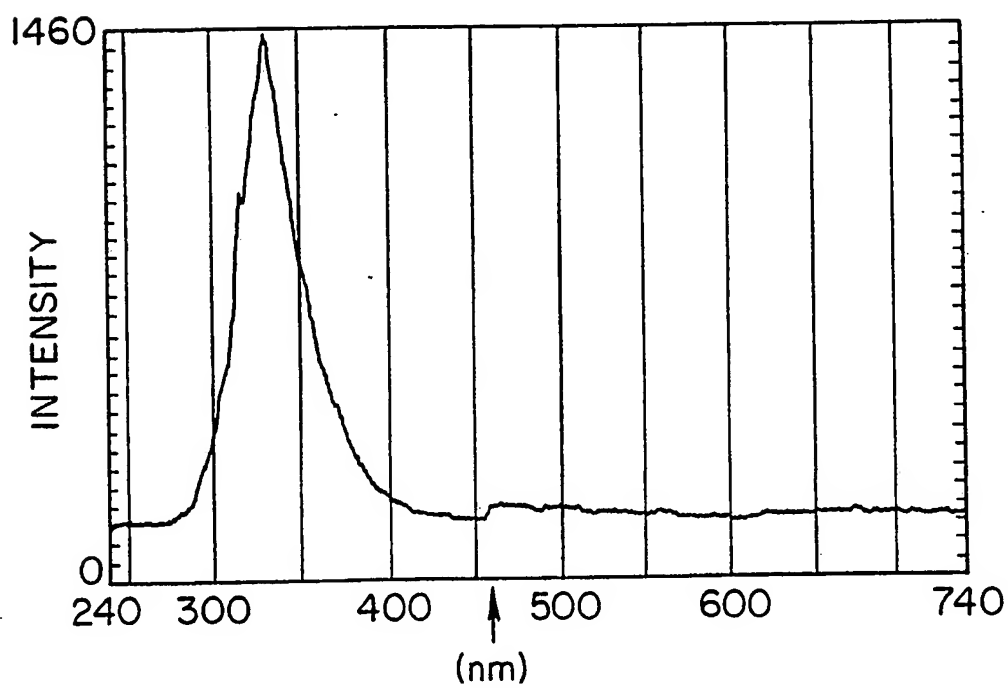
6/11



*Fig. 11*



*Fig. 12*

*Fig. 13**Fig. 14*

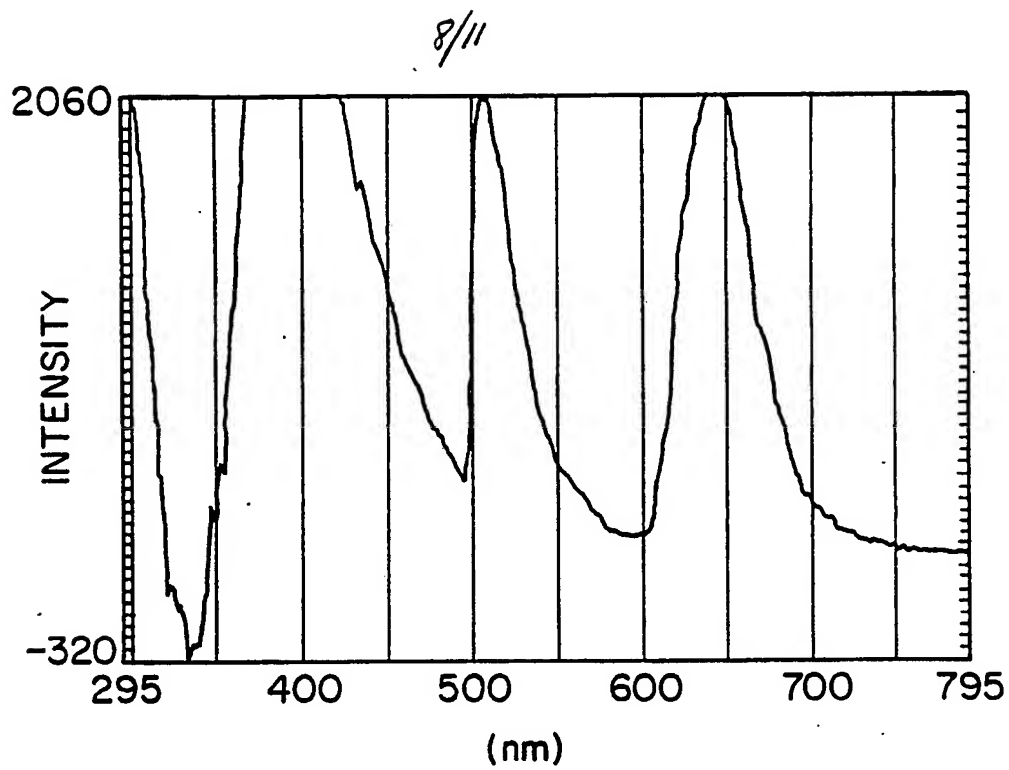


Fig. 16

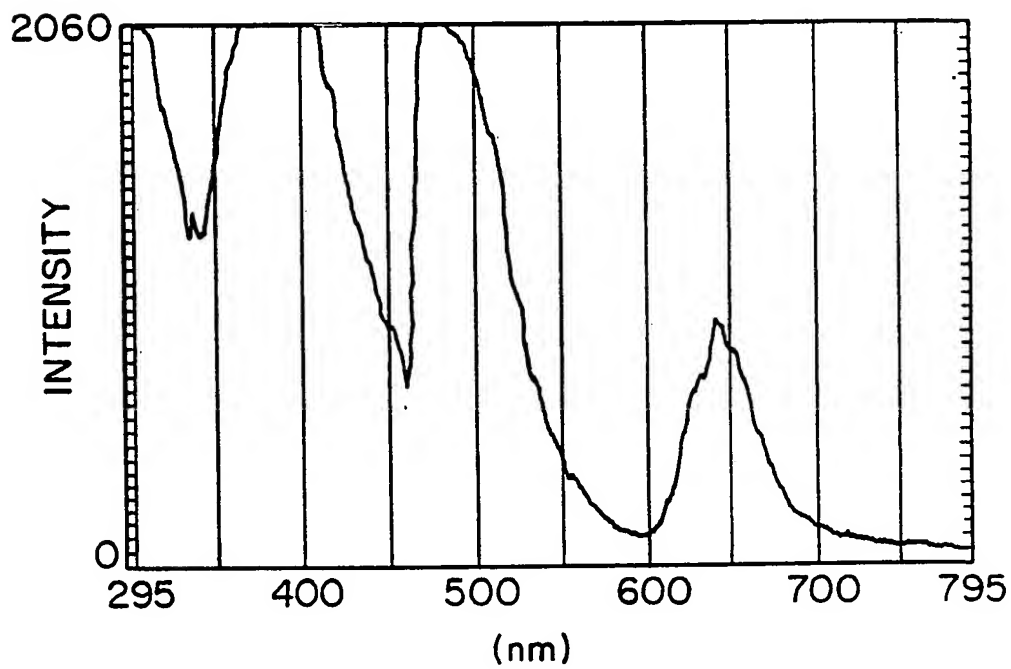
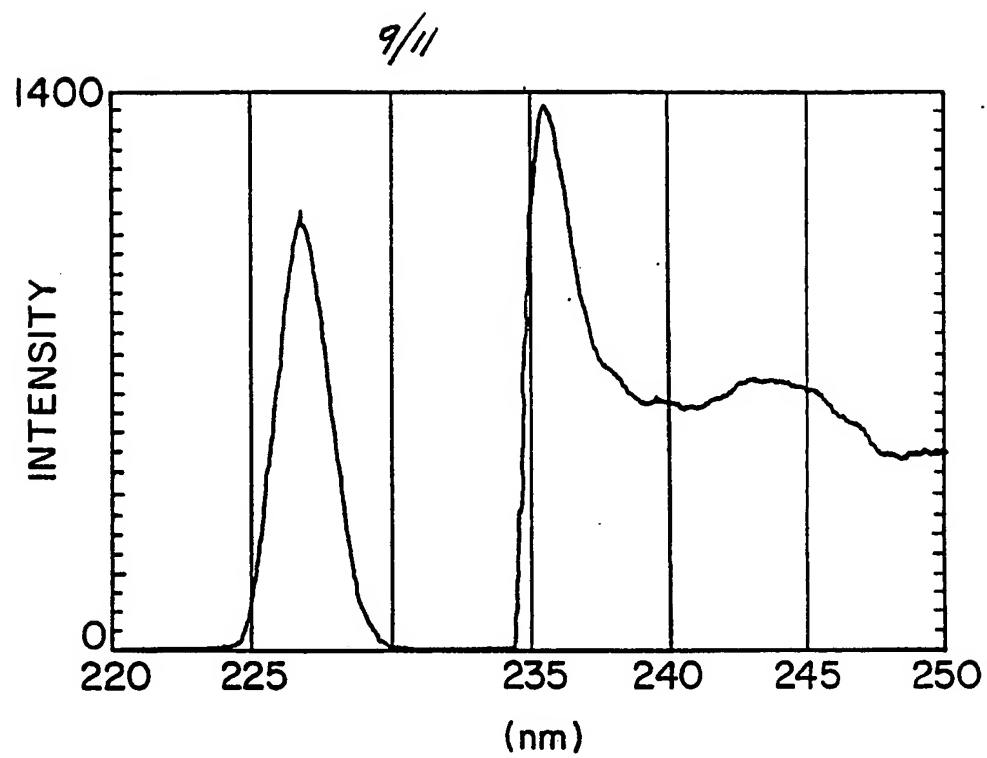
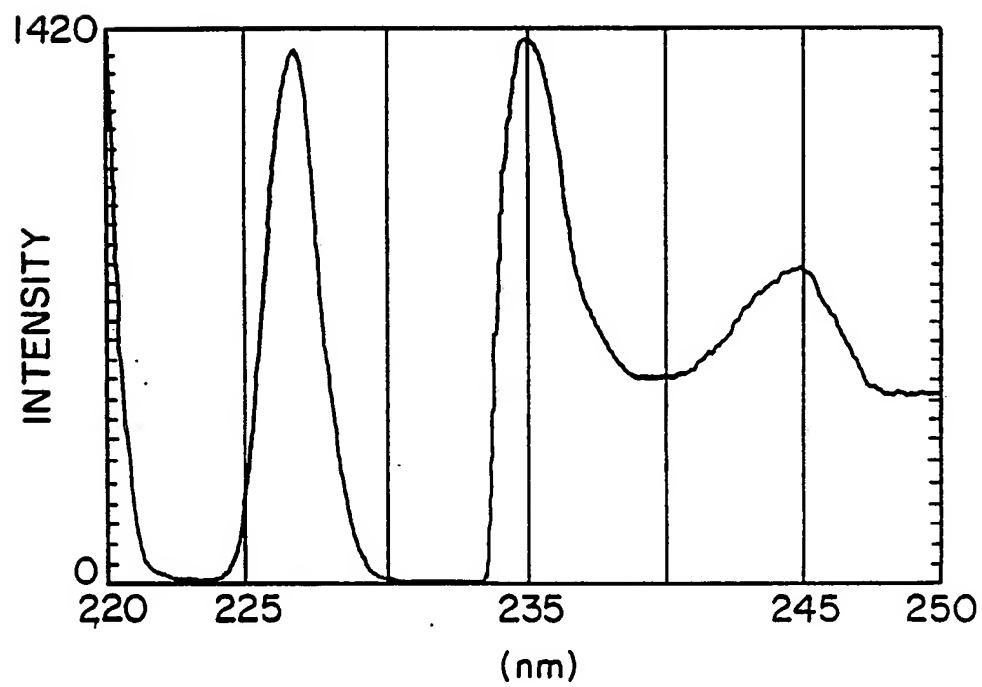


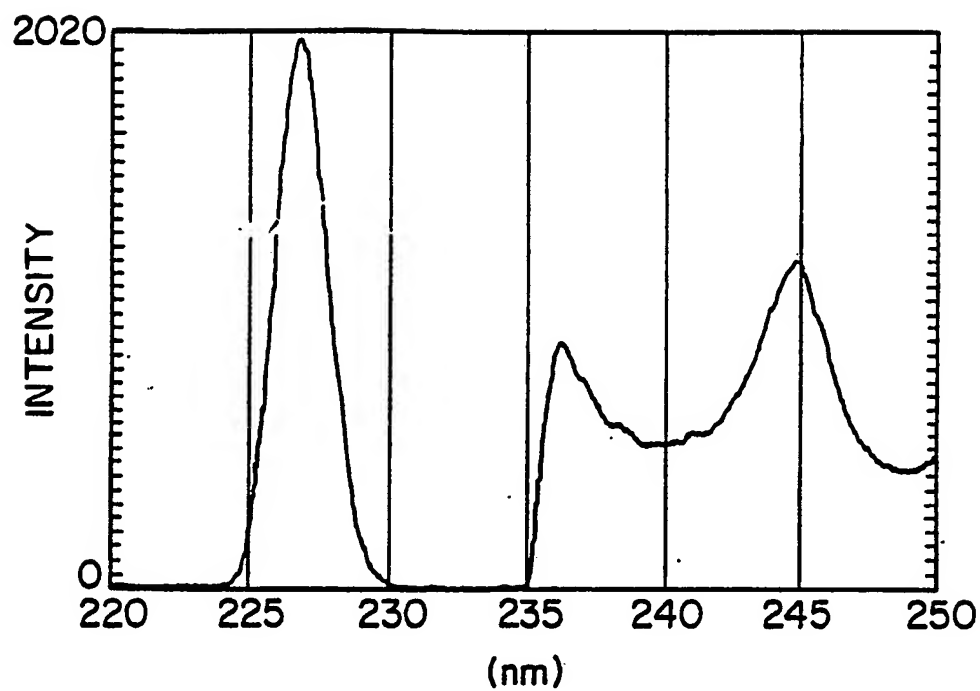
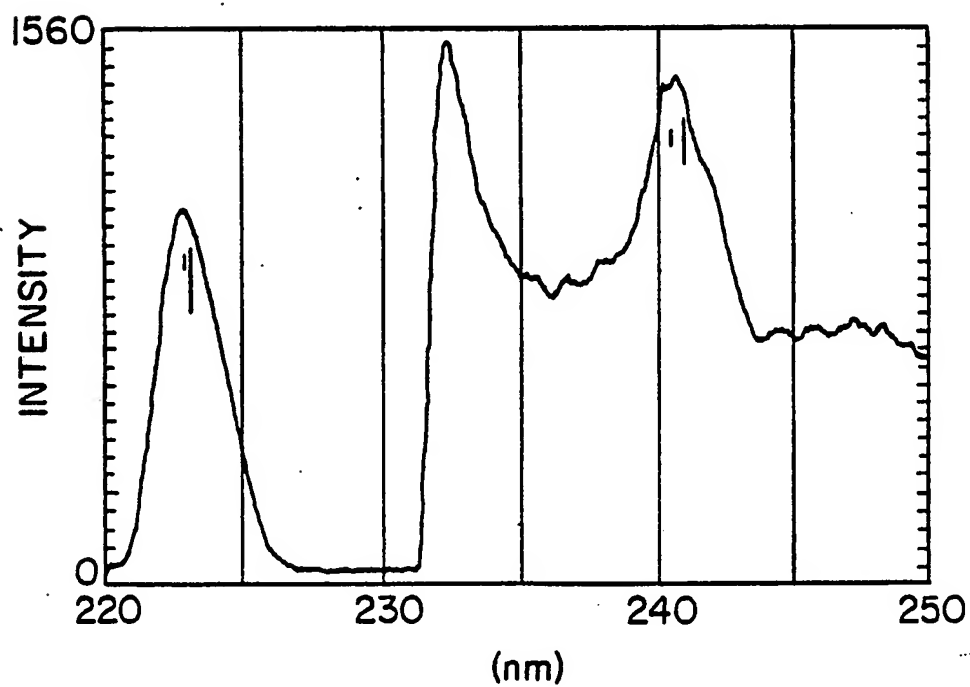
Fig. 15

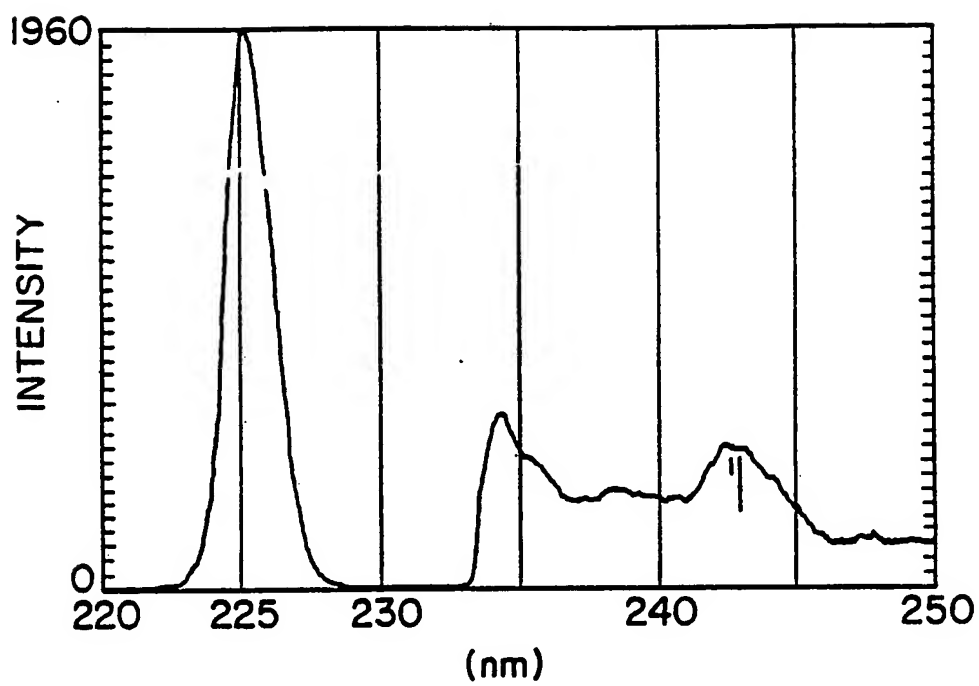
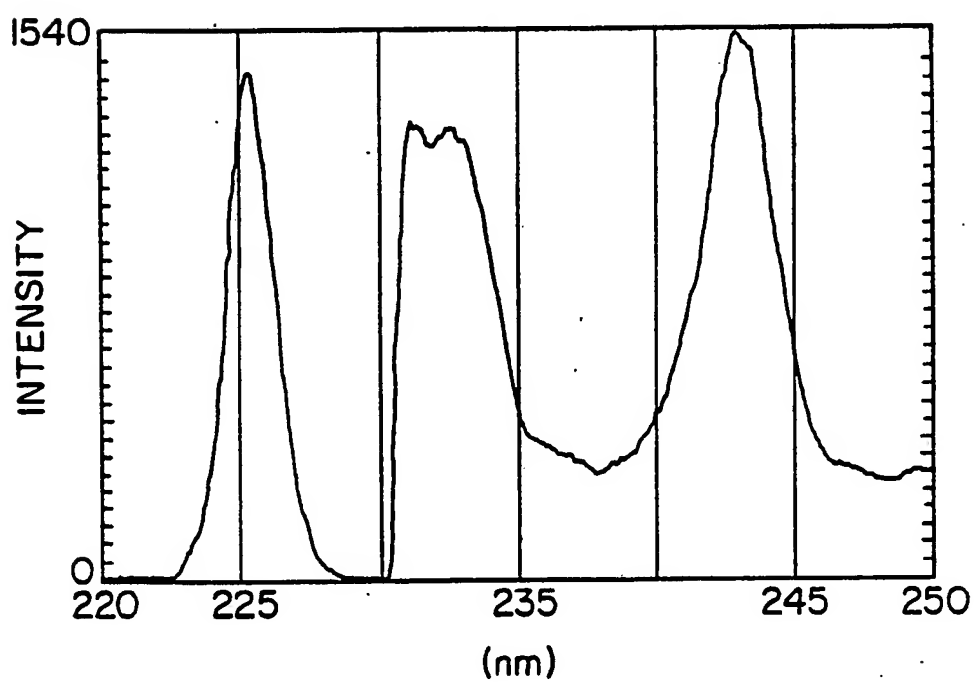


*Fig. 18*



*Fig. 17*

*Fig. 19**Fig. 20*

*Fig. 21**Fig. 22*



# INTERNATIONAL SEARCH REPORT

International Application No PCT/US 88/03257

<b>I. CLASSIFICATION OF SUBJECT MATTER</b> (if several classification symbols apply, indicate all) <sup>6</sup> According to International Patent Classification (IPC) or to both National Classification and IPC <b>IPC4: A 61 B 1/06</b>											
<b>II. FIELDS SEARCHED</b> <div style="text-align: right; margin-right: 100px;">Minimum Documentation Searched <sup>7</sup></div> <table style="width: 100%; border: none;"> <tr> <td style="width: 20%; border: none;">Classification System  </td> <td style="border: none;">Classification Symbols</td> </tr> <tr> <td style="border: none; padding-top: 10px;"><b>IPC4</b></td> <td style="border: none; padding-top: 10px;"><b>A 61 B, G 02 B, G 01 J</b></td> </tr> </table> <div style="text-align: center; margin-top: 10px; font-size: small;">             Documentation Searched other than Minimum Documentation              to the extent that such Documents are included in the Fields Searched <sup>8</sup> </div>			Classification System	Classification Symbols	<b>IPC4</b>	<b>A 61 B, G 02 B, G 01 J</b>					
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<b>IPC4</b>	<b>A 61 B, G 02 B, G 01 J</b>										
<b>III. DOCUMENTS CONSIDERED TO BE RELEVANT <sup>9</sup></b> <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="width: 10%; text-align: left; padding: 5px;">Category <sup>9</sup></th> <th style="width: 60%; text-align: left; padding: 5px;">Citation of Document, <sup>11</sup> with indication, where appropriate, of the relevant passages <sup>12</sup></th> <th style="width: 30%; text-align: left; padding: 5px;">Relevant to Claim No. <sup>13</sup></th> </tr> </thead> <tbody> <tr> <td style="vertical-align: top; padding: 5px;"><b>A</b></td> <td style="padding: 5px;">US, A, 4494823 (YOSHIDA ET AL) 22 January 1985, see column 1, line 5 - column 2, line 9; column 5, line 17 - line 43; abstract; figures 1,6 --</td> <td style="vertical-align: top; padding: 5px; text-align: center;">1-10</td> </tr> <tr> <td style="vertical-align: top; padding: 5px;"><b>A</b></td> <td style="padding: 5px;">US, A, 4163148 (FRITSCH ET AL) 31 July 1979, see the whole document -- -----</td> <td style="vertical-align: top; padding: 5px; text-align: center;">1-10</td> </tr> </tbody> </table>			Category <sup>9</sup>	Citation of Document, <sup>11</sup> with indication, where appropriate, of the relevant passages <sup>12</sup>	Relevant to Claim No. <sup>13</sup>	<b>A</b>	US, A, 4494823 (YOSHIDA ET AL) 22 January 1985, see column 1, line 5 - column 2, line 9; column 5, line 17 - line 43; abstract; figures 1,6 --	1-10	<b>A</b>	US, A, 4163148 (FRITSCH ET AL) 31 July 1979, see the whole document -- -----	1-10
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<b>A</b>	US, A, 4163148 (FRITSCH ET AL) 31 July 1979, see the whole document -- -----	1-10									
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p><sup>10</sup> Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"A" document member of the same patent family</p> </div> </div>											
<b>IV. CERTIFICATION</b> <table style="width: 100%; border: none;"> <tr> <td style="width: 50%; border: none; padding: 5px;">                 Date of the Actual Completion of the International Search  <b>7th February 1989</b> </td> <td style="width: 50%; border: none; padding: 5px;">                 Date of Mailing of this International Search Report  <b>0 6 MAR 1989</b> </td> </tr> <tr> <td style="border: none; padding: 5px;">                 International Searching Authority  <div style="text-align: center; margin-top: 10px;"><b>EUROPEAN PATENT OFFICE</b></div> </td> <td style="border: none; padding: 5px;">                 Signature of Authorized Officer  <div style="text-align: center; margin-top: 10px;"> <b>P.C.G. VAN DER PUTTEN</b> </div> </td> </tr> </table>			Date of the Actual Completion of the International Search <b>7th February 1989</b>	Date of Mailing of this International Search Report <b>0 6 MAR 1989</b>	International Searching Authority <div style="text-align: center; margin-top: 10px;"><b>EUROPEAN PATENT OFFICE</b></div>	Signature of Authorized Officer <div style="text-align: center; margin-top: 10px;"> <b>P.C.G. VAN DER PUTTEN</b> </div>					
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